DECLARATION OF MARIO A. GONZÁLEZ, Ph. D.

I, Mario A. González, Ph.D., hereby declare as follows, under penalty of perjury of the laws of the United States:

1. I am President and Chief Executive Officer of P'Kinetics International, Inc., a consulting firm specializing in pharmaceutical product development and pharmacokinetics research. I also am Adjunct Professor at the University of Florida, College of Pharmacy. *See* http://www.cop.ufl.edu/departments/pc/adjunct_faculty.htm. I was previously President of GloboMax Américas and prior to that was Director of Biopharmaceutics and Pharmacokinetics at Schering Research, Miami (formerly Key Pharmaceuticals, Inc), where I was actively involved in the development and evaluation of transdermal drug delivery systems. My research has concentrated on the pharmacokinetic and pharmacodynamic evaluation of extended-release oral and transdermal drug delivery systems as well as in vitro/in vivo correlations. Prior to joining the pharmaceutical industry, I was on the Pharmacy faculty at Purdue University with teaching and graduate research responsibilities in clinical pharmacokinetics. I have been active in the American Association of Pharmaceutical Scientists ("AAPS") since its inception and was Chair of the Pharmacokinetics Section in 1995. I also served on the organizing committees of the first four AAPS/FDA SUPAC Workshops and was Co-Chair of the Organizing Committee for the first Pharmaceutical Congress of the Americas held in March, 2001. I am also a member of the Controlled-Release Society, the American College of Clinical Pharmacology, and the American Society of Health-System Pharmacists, and I serve on the editorial advisory boards of the European Journal of Pharmaceutics and Biopharmaceutics and the International Journal of Clinical

Pharmacology and Therapeutics. My educational and professional background and a list of my publications are set forth in greater detail in my *curriculum vitae*, a copy of which accompanies this declaration.

2. I have been asked by Mylan Technologies Inc. ("Mylan") to provide my analysis and opinions in connection with a Citizen Petition submitted to the Food and Drug Administration by Steven L. Shafer, M.D., Docket No. 2004P-0340. Neither I nor any member of my family is or has been employed by Mylan or any of its affiliated companies, nor do I or any member of my family own any stock in Mylan or any of its affiliated companies. I have not consulted for Mylan, but I was retained by attorneys for Mylan to testify as an expert witness in patent litigation involving Mylan's fentanyl transdermal system. I also have consulted for the RW Johnson Research Institute of Johnson and Johnson (the parent of Alza Corporation, the NDA holder for Duragesic® fentanyl transdermal system), but not on any transdermal issues or fentanyl.

3. I have carefully considered the Citizen Petition submitted by Dr. Shafer, especially his conclusion that generic fentanyl transdermal systems that do not employ a so-called "rate-controlling membrane" may deliver unacceptably high doses of the drug when applied to "stripped" skin. For the reasons set forth below, I disagree with that conclusion.

4. Dr. Shafer compares two studies performed by different investigators, at different times, in different patients with different products. Specifically, Dr. Shafer compares results of the Varvel *et al.* study [3] involving Duragesic® fentanyl transdermal system with those of the Fiset *et al.* study [4] involving an experimental fentanyl transdermal product developed by Cygnus. (Numbers in brackets refer to references

listed at the end of this declaration.) He erroneously concludes that the amount of drug delivered by the Cygnus patch was highly variable and relies on a speculation by the authors that this variability might have been attributable to the application of some of the patches to skin that had been stripped by the removal of surgical tapes and the like. I have studied the data reported in both publications and disagree with Dr. Shafer's conclusions.

5. Comparison of the results of the Varvel *et al.* and Fiset *et al.* studies is of very questionable and limited value, given that these studies did not involve controlled, side-by-side evaluation of the two products. For the reasons explained herein, it is my opinion that the data reported by Fiset *et al.* was no more variable than that observed in the Varvel *et al.* study or that is typical of studies of comparable size using transdermal drug delivery systems. It also is my opinion that the somewhat higher blood levels observed in the Fiset *et al.* study were a result of the differences in the designs of the products and the fact that the Cygnus product delivered a significantly higher transdermal dose. These studies do not support the conclusion that some of the Cygnus patches delivered higher dosages of drug because of their application to stripped skin.

6. Transdermal dosing has always been a difficult parameter to measure, yet knowing the dose delivered from any formulation is critical to the proper use of a drug delivery system. For a solid oral dosage form, the administered dose is simply the amount of drug contained in the tablet or capsule. This is not the case with transdermal dosage forms, and labeling the total content in a transdermal product as the dose would be misleading for both the patient and the health care provider. The FDA addressed this problem by requiring that all transdermal products be labeled in terms of their delivery

rates (quantity delivered/time). For example, the Agency initially required that the nitroglycerin products be labeled with the dose delivered over 24 hours. Later the Agency required labeling that indicated the dose delivered per hour.

7. The dose delivered by a transdermal product has been expressed as the Apparent Dose [1, 2] and is calculated experimentally from transdermal systems that have been applied to patients or healthy volunteers. The calculation is a simple one and is summarized by the following relationship:

Apparent Dose = Initial Potency – Residual Potency

where Initial Potency refers to the amount of drug contained in a transdermal system prior to application to a volunteer, and Residual Potency is the amount of drug remaining in the delivery system after application for the duration of the dosing interval. The advantage of this determination for fentanyl is that it relies on measuring mg amounts of drug which facilitates the assay and it does not require any sophisticated mathematics or assumptions.

8. In the 1989 Varvel *et al.* publication dealing with intravenous fentanyl and Duragesic®, the authors stated, "[a]n important assumption in the design of this study was that fentanyl clearance would not change from the intravenous study to the transdermal study. General anesthesia may be associated with a decrease in hepatic blood flow or enzyme activity and might be expected to decrease fentanyl clearance." [3]. Obviously, I concur with this observation and agree that such an assumption could lead to errors in pharmacokinetic calculations that depend on a constant clearance. A decrease in clearance would result in higher blood levels even if the dose absorbed remained the same. It is well known that fentanyl is metabolized by liver enzymes and that

metabolism can be affected by a variety of external influences, including surgery, diet, stress, etc. Fentanyl blood levels, therefore, can be attributable to a number of factors, including the rate of fentanyl metabolism and clearance, and do not necessarily indicate differences in input rates alone.

9. In the Varvel *et al.* study of Duragesic®, the dose delivered (the Apparent Dose) was calculated by the residual method and reported in Table 2 of the paper [3]. The individual values are reported in that table and are identified as "Dose delivered = total amount of fentanyl lost from the transdermal system by residual analysis after removal of system at 24h." Table 1 below lists the individual values as well as the arithmetic mean, the standard deviation, and the coefficient of variation (100 X (SD/mean)). A similar value was calculated for the Cygnus fentanyl transdermal product and reported by Fiset *et al.* in Table 3 of their publication [4]. These results are listed in Table 2 along with the summary statistics. As these data demonstrate, the mean Apparent Dose from Duragesic® ± SD was 3.41±0.87 mg/24h (25.5% CV). The mean Apparent Dose from the Cygnus product, however, was 4.96±1.04 mg/24h (21.0% CV). While the variability of the absorbed dose was similar for the two products (25.5% vs. 21.0%), the absorption from the Cygnus transdermal system was substantially higher. Figures 1 and 2 illustrate the differences in Apparent Dose between the products while demonstrating a similar interpatient variability in absorption.

10. Varvel *et al.* noted the variability and explained that, "...interindividual variability in serum fentanyl concentrations is significant following placement of the transdermal fentanyl system. This variability is partially due to the large interindividual variability in iv fentanyl pharmacokinetics and partially due to interindividual variability

in transdermal absorption characteristics" [3]. Variability in absorption from transdermal products is not unique for fentanyl and has previously been discussed for other drugs [2].

11. While there is no crossover study information comparing the Cygnus fentanyl product to Duragesic® in the same patients, the data reported in References 3 and 4 clearly demonstrate a 45% greater absorption of fentanyl from the Cygnus product. It should be noted that while the Citizen Petition compares Duragesic and the Cygnus fentanyl product, the two delivery systems were designed with different goals. Duragesic is intended to be applied for 72 hours, while the Cygnus product appears to have been targeted for 24-hour delivery. This higher absorption was by design, because the product was "...specifically developed for postoperative analgesia..." [4], an indication for which Duragesic is not approved.

12. The results reported by Fiset *et al.* [4] demonstrate that the Cygnus product could not have been bioequivalent to Duragesic®, although the Citizen Petition implies that the Cygnus product was a candidate for approval as a generic. For the FDA to approve generic fentanyl transdermal delivery systems, bioequivalence to Duragesic® must be demonstrated on healthy, undamaged skin, so as to allow the conduct of well-controlled, crossover bioavailability studies. Skin-stripping prior to a bioavailability study would only add an additional variable that would make a true crossover study more difficult to complete, because the skin would have to be seriously damaged in order to test the theory presented by the Citizen Petition. It is not logical, therefore, to utilize data from the Cygnus transdermal fentanyl to support an argument against the FDA's approval of ANDA's for generic transdermal fentanyl. While the Citizen Petition suggests that the higher levels seen after dosing with the Cygnus product were due to

skin stripping, it is reasonable to conclude that higher levels were observed because higher doses were administered.

Signed this 20th day of August, 2004 in Pembroke Pines, Florida.

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References

1. P.K. Noonan, M.A. González, et al.: Relative Bioavailability of a New Transdermal Nitroglycerin Delivery System, *J. Pharm. Sci.*, *75*, 688-691, 1986.

2. M.A. González, Trends in Transdermal Drug Delivery, Chapter 8 in "Topics in Pharmaceutical Sciences," 1991, D.J.A. Crommelin and K.K. Midha (Eds.), Medpharm Scientific Publishers, Stuttgart, 1992.

3. J.R. Varvel, S.L. Shafer, et al.: Absorption Characteristics of Transdermally Administered Fentanyl, *Anesthesiology, 70*, 928-934, 1989.

4. P. Fiset, C. Cohane, et al.: Biopharmaceutics of a New Transdermal Fentanyl Device, *Anesthesiology, 83*, 459-469, 1995.

Table 1. Fentanyl Apparent Dose from Duragesic® [3]

Patient	Apparent Dose
1	4.75
2	2.32
3	4.28
4	3.51
5	2.48
6	3.17
7	3.94
8	2.83
Mean, mg	3.41
SD	0.87
CV,%	25.5
flux/h, mg	0.142

Table 2. Fentanyl Apparent Dose from Cygnus Transdermal [4]

Patient	Apparent Dose
1	3.24
2	Inc
3	6.48
4	4.18
5	4.22
6	6.53
7	5.58
8	4.60
9	5.43
10	NA
11	4.50
12	4.90
13	Inc
14	Inc
15	NA
Mean, mg	4.96
SD	1.04
CV,%	21.0
flux/h, mg	0.207

Inc = Incomplete dosing interval; patches removed prior to 24h
NA = Data not available; #10 not enrolled, no residual data for #15

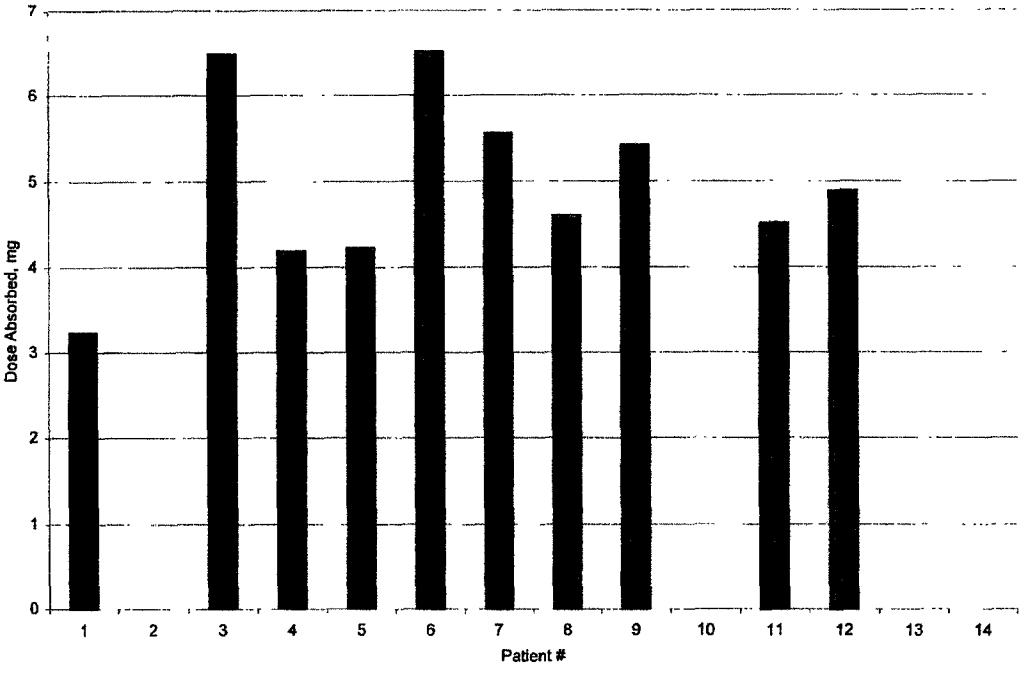

Figure 1. Apparent Dose from residual fentanyl in Cygnus transdermal system after dosing for 24 hours. Patients 2, 10, 13, 14 & 15 did not complete protocol.

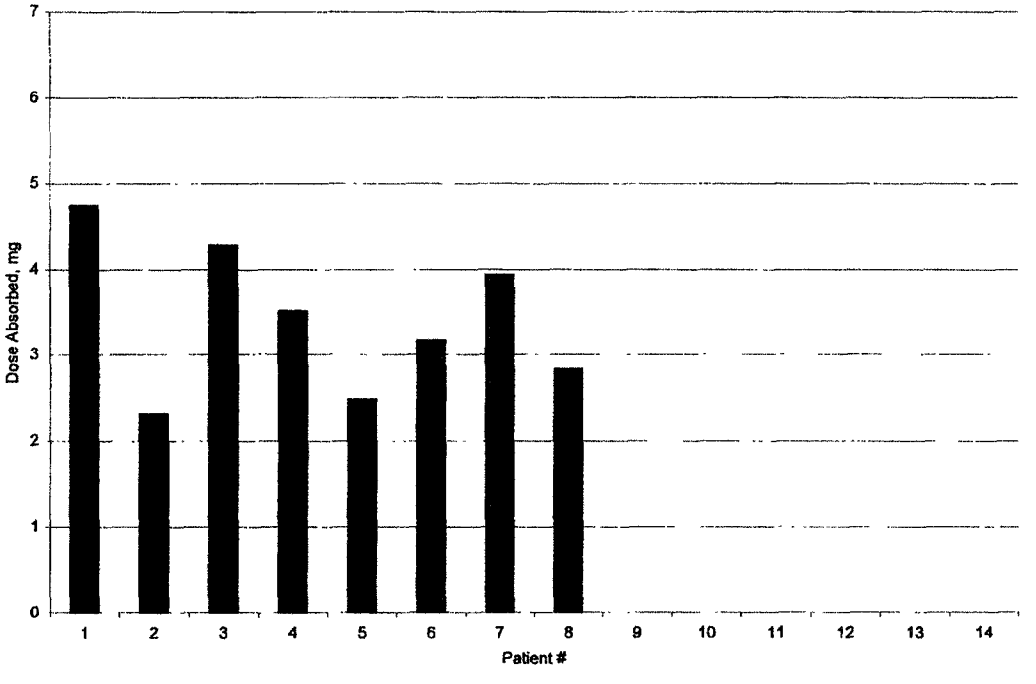

Figure 2. Apparent Dose from residual fentanyl in Duragesic after 24 hours.